Our skeleton is constantly renewed at an average rate of 10% per year. Osteoporosis is a disease resulting from a decreased renewal of bone, which leads to a fragile skeleton and increased risk of fractures. The etiology of osteoporosis is complex in the sense that the fracture risk is influenced by genetic and environmental factors, with lifestyle becoming more important with increasing age [1]. Typical osteoporotic fractures include the hip, vertebral, proximal upper arm, and distal forearm. Such fractures not only entail high health care costs but also are frequently associated with loss of quality of life because of deficient healing. Furthermore, osteoporotic fractures carry an increased risk of mortality.

Several modifiable risk factors with respect to osteoporotic fractures have been proposed. As such, calcium supplementation or the consumption of calcium-rich foods (such as dairy products) is commonly recommended for the prevention of osteoporosis and fractures. However, the influence and importance of dietary calcium intake in primary prevention of osteoporotic fractures have been under a long and intensive debate. Contrary to common beliefs, the conclusions that can be drawn from previous studies are far from unequivocal. Adding to the number of non-expected findings in this issue of *Nutrition*, Zhong et al. [2] found no overall association between fracture risk and dietary and supplemental calcium intake. The carefully conducted analysis was performed in the National Health and Nutrition Examination Survey cohort that included 2000 community-dwelling postmenopausal women. Of these 2000 women, 237 reported a fracture of their hip, spine, or wrist during follow-up.

Large studies are needed to provide robust proof of a relation because the effect of calcium on fracture risk is likely to be modest. Nevertheless, a recent meta-analysis [3] of all prospective cohort studies, including more than 3000 hip fractures, revealed no significant fracture risk reduction with increasing calcium intake. This general lack of effect has several possible explanations. First, there might not be a major association between dietary calcium intake in middle-aged and elderly women and osteoporotic fracture risk because the calcium content of the food in the Western diet is sufficient to meet the structural and functional demands of the skeleton. Second, the association between calcium intake and fracture risk might be non-linear, i.e., the decrease or increase in risk may be concentrated to extreme intakes. These threshold effects might not be readily discovered in even large studies, primarily because of the small number of subjects at the extreme ends of calcium intake. Third, renal losses of calcium and the intestinal capacity for calcium absorption can be more important determinants of osteoporosis than the dietary content of calcium. Fourth, calcium intake cannot be regarded in isolation. Other nutrients that interact with calcium intake or affect bone mass or postural stability must also be considered in the analysis. In this respect, Zhong et al. found that the effect of calcium intake on fracture risk was modified by the total protein intake. Their results are intriguing and provoke important questions about the complex relation among calcium intake, dietary protein, and fracture risk. Nevertheless, the interplay between dietary protein and calcium intake needs further evaluation in future larger studies. Fifth, it has been argued [4] that there is a considerable bias in dietary calcium assessment that can lead to a decreased ability to demonstrate associations. Notwithstanding, the relatively strong correlation ($r = 0.60–0.75$) between calcium intake estimated from different methods in observational studies, including the human fat tissue content of pentadecanoic acid that is a biomarker of dairy fat consumption [5,6], provides a strong argument against a substantial influence of this bias.

Measurement error of the exposure is less of a problem in interventional trials. Several randomized studies have also shown that calcium supplements can retard bone loss [7,8]. The question of whether the observed preservation of bone by calcium supplements is a transient or a steady-state effect has been exhaustively explored. Bone is constantly renewed but the rate of the remodeling process is not evenly distributed throughout the skeleton. It is higher in cancellous bone, which is more abundant in the vertebrae and in the metaphyseal regions of the long bones (i.e., the osteoporotic fracture-relevant sites) than in cortical bone. An increased intake of calcium suppresses the number of bone-remodeling sites, leading to an apparent increase in bone density. Several studies have also observed that the rate of bone loss is significantly lower in the first years of calcium supplementation, especially at regions where more than half of the bone content is of the cancellous type [9,10]. The long-term effect of additional dietary calcium on bone density
and fracture prevention is therefore not readily revealed by or extrapolated from randomized bone density studies.

Importantly, calcium trials with fracture as outcome are inconsistent. Two recent meta-analyses have concluded a slightly lower risk, no risk, or even an increased risk of osteoporotic fractures with calcium supplements [3,7]. Unfortunately, no trial with a factorial design has addressed the impact of calcium supplements with the customary dietary intake of calcium on the risk of osteoporotic fractures.

Consequently, the recommended acceptable threshold for dietary calcium intake or for calcium pharmacologic supplementation remains unclear. Current recommendations range from 400 to 1500 mg/d, which is an indication that no firm conclusions from the current body of scientific evidence can be drawn. Therefore, a general recommendation to middle-aged and older community-dwelling citizens to increase their calcium intake by diet or supplements in isolation to decrease their future risk of osteoporotic fracture cannot be recommended.

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References